UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,567	11/13/2003	Qun-Yong Zhou	UCI1240-3	8395

7590 08/07/2006

LISA A. HAILE, J.D., PH.D.
DLA PIPER RUDNICK GRAY CARY US
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133

EXAMINER	
DANG, IAN D	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/713,567	ZHOU, QUN-YONG	
	Examiner	Art Unit	
	Ian Dang	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-48 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-48 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-48 are pending and under examination.

Priority

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting; Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/016,481 fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The claimed invention drawn to a method of modulating angiogenesis comprising administering an amount of prokineticin receptor antagonist to alter angiogenesis wherein the prokineticin receptor antagonist comprising an amino sequence of the SEQ ID Nos 3 and 6. The amino acid sequences of the SEQ ID NO:3 and 6 are not disclosed in the U.S. provisional application 60/245,882 but are disclosed in U.S. application 10/016,481 filed on 11/01/2001. Therefore, the instant application gets the priority of the U.S. application 10/016,481 filing date of 11/01/2001

Claim Rejections - 35 USC § 112 (Written Description)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims 1-48 are drawn amino acid sequences that are at least 80% identical to amino acids to 7 to 77 of SEQ ID NO:3 and at least 80% identical to amino acids to 7 to 77 of SEQ ID NO:6.; these 2 claims are thus genus claims. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claims do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to the encoded prokineticin variant. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the nucleic acid class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID N0: 3 encoding the polypeptide or SEQ ID NO: 6 are insufficient to describe the genus.

The written description requirement for a claimed genus' may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or

other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polypeptides.

There is no description of the conserved regions, which are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed by the limitations. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus. Very nice!

Claim Rejections - 35 USC § 112 (Enablement)

Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of binding to prokineticin receptor 1 and decreasing endothial cell growth *in vitro* comprising administering amino acid SEQ ID NO:3 encoding the prokineticin receptor antagonist for *in vitro* cellular assays including receptor antagonist, migration and angiogenic assays with endothelial cells, does not reasonably provide enablement for a method of modulating angiogenesis in any tissues or animals with any angiogenesis dependent diseases including cancer. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include: (1) Nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the breath of the claims, (7) the quantity of experimentation needed, (8) relative skill of those in the art.

Nature of the invention and breath of the claims

The claims are drawn to a method of modulating angiogenesis comprising administering an amount of prokineticin receptor antagonist. The invention encompasses effecting increases and decreases in angiogenesis with prokineticin receptor antagonists having amino acid sequences SEQ ID NO:3 and SEQ ID NO:6. in any cells or tissues, including cells and tissues associated with cancer. Therefore, the claims encompasses administration of the antagonists *in vivo* as cancer therapeutics.

The unpredictability of the art and the state of the prior art

The search in the polypeptide database reveals that PK1 receptor antagonist with amino acid SEQ ID NO:3 is 100% identical to the amino acid encoded by EG-VEGF disclosed by LeCouter et al. (2001). LeCouter et al. recite that EG-VEGF is a mitogen not only specific to endothelial cells, but also acting selectively on a defined type of endothelial cells (page 878, 2nd paragraph). In addition, EG-VEGF is able to induce the formation of new blood vessels in an ovarian cyst. Furthermore, LeCouter et al. teach that intra-ovarian delivery of either EG-VEGF or VEGF adenovirus resulted with a week in a dramatic enlargement of the injected ovaries and

that the partially complementary expression patterns of VEGF and EG-VEGF indicate that these molecules may function in a coordinated or complementary manner to regulate angiogenesis. While Applicants disclose that PK1 inhibits proliferation of endothelial cells in examples II and III , LeCouter et al. teach that an identical polypeptide to the PK1 receptor antagonist, EG-VEGF, promotes the proliferation of ACE endothelial cells. Thus PK1 induces conflicting effects on endothelial cells.

In addition, prokineticin 1 has an amino acid sequence identical to PK 1 and prokineticin 2 has amino sequences identical PK2 disclosed in the specification on pages 9 and 10. Li et al. (2001) recite that sequence analysis reveals that prokineticins 1 and 2 contain all 10 conserved cysteines and have about 44% amino acid identity. In addition both prokineticins were widely expressed in various adult and fetal tissues, with a generally higher expression level of prokineticin compared with prokineticin 2 (page 694, column 1, 1st and 2nd paragraph). These teachings disclose that prokineticins have different structures and different tissue distribution. In light of the differences between PK1 and PK2, these 2 PK receptor antagonists also have different biological functions despite the disclosure in specification teaching that PK1 and PK2 competes with each other binding to receptors (see figures 2 A-C).

The claims encompass the experimental and unpredictable field of *in vivo* therapy for cancer. Those of skill in the art recognize that, although *in vitro* assays are generally useful to screen the effects of agents on target cells, clinical correlation with treatment of a disease *in vivo* does not necessarily follow. The greatly increased complexity of *in vivo* therapy compared to the narrowly defined and controlled conditions of an *in vitro* assay does not permit a direct extrapolation of *in vitro* assay results to mammal or human therapy with any degree of predictiability. *In vitro* assays cannot adequately assess cell to cell interactions which may be important in a particular pathological state. Furthermore, a therapeutic agent must accomplish

several tasks to be effective; it must be delivered into circulation, it must interact at the proper site at a therapeutic concentration, and it must remain effective for a sufficient period of time. *In vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In an *in vitro* assay, the agent is in direct contact with target cells during the entire exposure period, whereas in *in vivo* therapy, exposure at the target site may be delayed and/or reduced. The composition may be inactivated *in vivo*, such as by proteolytic degradation or immunological inactivation, before producing the desired effect. See Jain et al., Cancer and Metatasis Review, vol. 9, pp. 253-266 and Dermer, Biotechnology 12:320, 1994, for a discussion of the differences between *in vitro* assay and *in vivo* therapy and the numerous pitfalls associated with *in vivo* cancer therapy.

The amount of direction or guidance present

Applicants' disclosure is limited to the use of PK1 in in vitro assays, including receptor and proliferation assays of endothelial cells. While the proliferation of endothelial cells is critical for angiogenesis, other biological processes contribute to the formation of new blood vessels including migration and tube formations of endothelial cells. The specification discloses only the first step of a long series of step needed for angiogenesis. Although Applicants disclose PK1 binds to PK1 receptors and decreases the proliferation of endothelial cells, the specification does not provide any guidance or direction regarding PK1 modulation of angiogenesis in vivo. In addition, the specification does not provide any guidance or direction regarding a method of modulating angiogenesis with of PK2 in any *in vitro* or *in vivo* assays.

Working Examples

The specification does not provide any examples enabling PK1 and PK2 for the modulation of angiogenesis. Although Applicants provide examples teaching that PK1 binding to PK1 receptors and inhibiting the proliferation of endothelial cells, Applicants have not

provided any examples enabling PK1 modulating angiogenesis *in vivo* or *in vitro*. In addition, Applicants have not provided any examples enabling PK2 for the modulation of angiogenesis. The specification discloses examples of PK2 in receptor ligand assay.

The quantity of experimentation needed

Because the claims are broadly drawn to a method of modulating angiogenesis comprising administering prokineticin receptor antagonists SEQ ID NO;3 or SEQ ID NO:6 both *in vitro* and *in vivo* and because Applicant's disclosure does not contain sufficient teachings to overcome the unpredictability taught in the art, it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 17-21 are rejected under 35 U.S.C. 102(b) as being anticipated by LeCouter et al. (published in August 30, 2001) provided in the IDS as number 56.

The claimed invention is drawn to a method of modulating angiogenesis comprising administering an amount of a prokineticin receptor antagonist effective to alter one or more indicia of angiogenesis, wherein said antagonist comprises an amino acid sequence at least 80% identical SEQ ID NO:3 and 6. The claimed invention is further drawn to administering the antagonist to an endothelial cell altering cell migration, cell survival; administering the antagonist to a tissue including cornea, chick chorioallantoic membrane, or any tissue; administering the antagonist to an animal including chicken, non-human primate, rat, mouse, and human;

administering the antagonist to animal having angiogenesis-dependent disease, wherein the disease is cancer.

The search in the polypeptide database reveals that SEQ ID NO:3 is 100% identical to the amino acid encoded by EG-VEGF disclosed by LeCouter et al. (2001).

When EG-VEGF is administered to human umbilical vein endothelial cells (HUVEC), the cells fail to migrate in the presence of EG-VEGF matching the limitations of claims 17 and 18 (page 878, column 2, 3rd paragraph). Moreover, EG-VEGF stimulates the proliferation of adrenal-cortex derived capillary endothelial (ACE) cells caused by increased survival matching the limitation of claim 19 (page 878, column 2, 1st paragraph). In addition, LeCouter et al. recite that purified EG-VEGF failed to show a significant response in the eyes tested in a rat or rabbit corneal pocket assay (page 880, column 2, 3rd paragraph) embracing the limitations of claims 21 and 22. Furthermore, EG-VEGF induces the fenestration, the formation of membrane discontinuities, of cell profiles of ACE cells encompassing the limitation of claim 20 (page 879, column 1, 1st paragraph).

Conclusion

No claims are allowed.

Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ian Dang whose telephone number is (571) 272-5014. The examiner can normally be reached on Monday-Friday from 9am to 5pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on

(571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ian Dang
Patent Examiner
Art Unit 1647
August 03, 2006

Brenda Brumback

BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600